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# A STUDY OF THE HOESCH REACTION

BY

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THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS  
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THE GRADUATE SCHOOL

May 9, 1922

I HEREBY RECOMMEND THAT THE THESIS PREPARED UNDER MY  
SUPERVISION BY Wilson Davis Langley  
ENTITLED A STUDY OF THE HOESCH REACTION.

BE ACCEPTED AS FULFILLING THIS PART OF THE REQUIREMENTS FOR  
THE DEGREE OF Doctor of Philosophy in Chemistry.

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The writer feels a deep sense of gratitude to Professor Roger Adams for his willing and patient guidance during three years at the University of Illinois, and in particular, for his direction in this research work.





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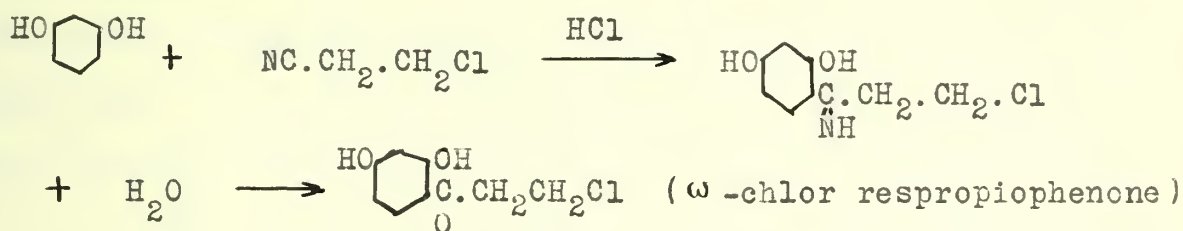


I. INTRODUCTION.

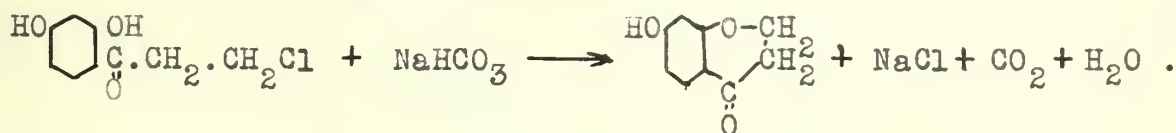


The condensation of phenolic compounds with nitriles has been carried out under different conditions, and occurs in two ways, depending upon the nature of the nitriles. The products obtained have been either ketones or lactones, and so far, little work has been done to determine the factors which influence the condensation to give one or the other type of compound. It was thought by the writer that a study of the Hoesch reaction, the condensation of nitriles with phenols by means of dry hydrogen chloride, which gives either ketones or lactones, would help to explain the nature of the condensation.

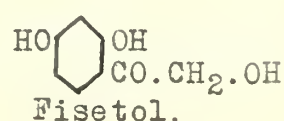
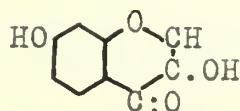
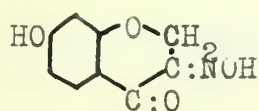
By the use of certain halogen substituted nitriles it ought to be possible, if compounds of a ketonic nature are obtained, to synthesize some important products which are found in nature, or which are obtained from natural products by chemical transformation. This can be seen from the theoretical equation:



Upon treatment of the ketone with a weakly basic substance such as pyridine or sodium bicarbonate, the halogen atom should split out as hydrochloric acid, as in the following scheme:



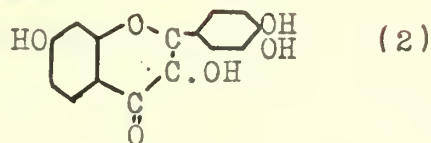
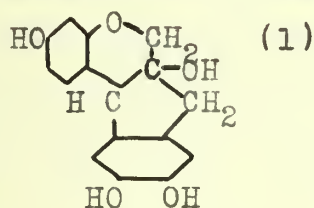
The 7-oxychromanone formed could be converted by well known reactions into the following compounds:

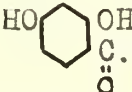




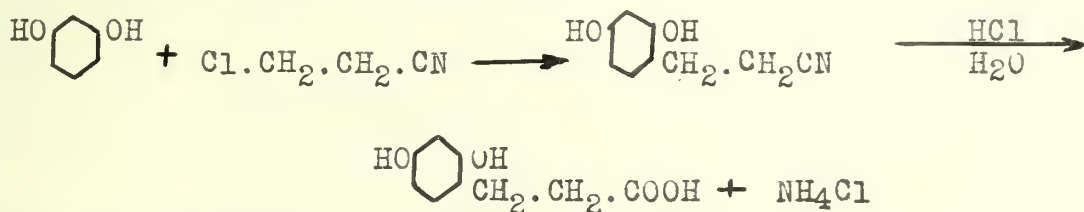


the second and third of which have been isolated from the decomposition products of braselin (1) and fisetin (2)



but which have never been synthesized. By the use of  $\gamma$ -chlorobutyronitrile ( $\text{Cl} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CN}$ ), it ought, theoretically, to be possible to isolate the corresponding chloroketones, and to prepare seven membered ring systems corresponding to the chromanones. By the use of ethylene cyanhydrin ( $\text{HO} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CN}$ ), it should be possible to synthesize a homologue of fisetol   $\text{C} \cdot \text{CH}_2 \cdot \text{CH}_2 \text{OH}$ . This compound, because of the longer side chain, should be more stable than, but should have chemical properties similar to those of fisetol itself. This nitrile would also be a means of preparing the compounds which are derived from  $\beta$ -chloropropionitrile with phenols, as the hydroxyl group ought to be readily replaceable by halogen, or removed in the form of water, by closure of the ring to give 7-oxychromanone.

If, on the other hand, the Hoesch reaction should go abnormally in the case of these nitriles, it ought to be possible through the following mechanism;



to synthesize certain phenolic acids which have been hitherto unknown or difficult to prepare. In addition, it ought to be possible to prove beyond doubt the mechanism of the Hoesch reaction.



For instance, if, as is assumed by one author, the halogen of the chlorimido group ( $R.CCl:NH$ ) reacted with the phenolic hydroxyl group, there might be obtained an ester of chlorpropionic acid, ( $Cl.CH_2.CH_2.COOR$ ), or, if the  $\beta$ -halogen then reacted, the lactone of a phenolic acid. If, on the other hand, the halogen in the  $\beta$  or  $\gamma$  positions of the nitrile reacted first, it should be possible to isolate the corresponding nitrile or amide of the acid.

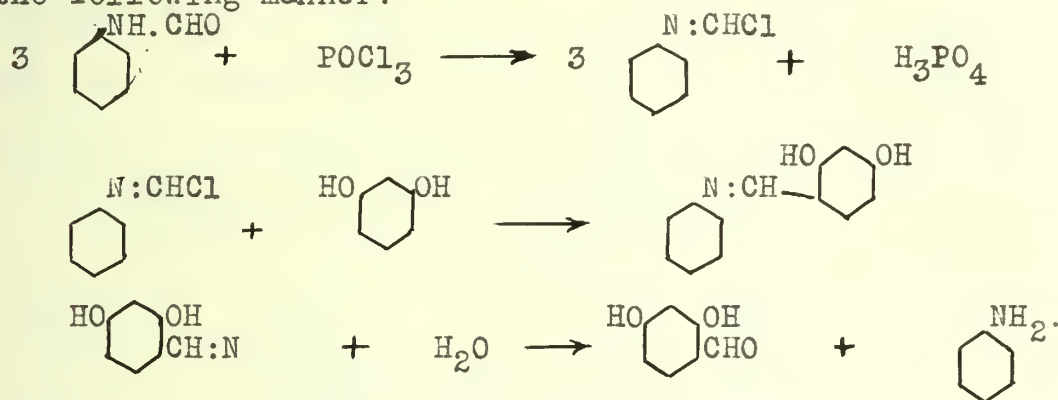
It would be of value also to determine whether or not the aliphatic unsaturated nitriles, such as acrylic nitrile ( $CH_2:CH.CN$ ) react in a manner similar to the aromatic unsaturated nitriles such as cinnamic nitrile, and p-coumaric nitrile, used by Fischer and Nouri in their attempt to synthesize flavones by means of the Hoesch reaction.

## II. HISTORICAL.

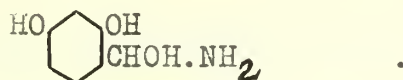
The first condensation of a nitrile with a phenol was accomplished by Bistrzycki<sup>(3)</sup>, who condensed mandelic nitrile and some of its derivatives with phenols by means of 73% sulphuric acid, and obtained a mixture of acids and lactones. The nitrile was used in place of mandelic acid to determine whether or not it would give an increased yield of lactone over that of the corresponding acid, and it was found that with the nitrile, the yield of lactone was 39-43%, and of the acid 15%, while with mandelic acid, the amount of lactone was 32%, and of the acid 39%. Simonis<sup>(4)</sup> then prepared a number of lactones from mandelic acid and  $\beta$ -naphthol, using mandelic acid instead of the nitrile because it was easier to prepare..



Dimroth<sup>(5)</sup> in 1902 discovered that when benzanilide-imidochloride  $\text{C}_6\text{H}_5\text{N}:\text{C}(\text{Cl})\text{C}_6\text{H}_5$  reacted with dimethyl-aniline, there was obtained the phenyl-imine of dimethyl-aminobenzophenone  $\text{C}_6\text{H}_5\text{N}(\text{CH}_3)_2\text{C}=\text{C}_6\text{H}_5$  and that when formaldehyde-aniline ( $\text{C}_6\text{H}_5\text{NH}.\text{CHO}$ ) was condensed with phenols by means of phosphorus oxychloride in dry ether, there was obtained an anilide, which on warming with dilute alkali hydrolyzed to the corresponding aldehydes. The condensation was explained in the following manner:

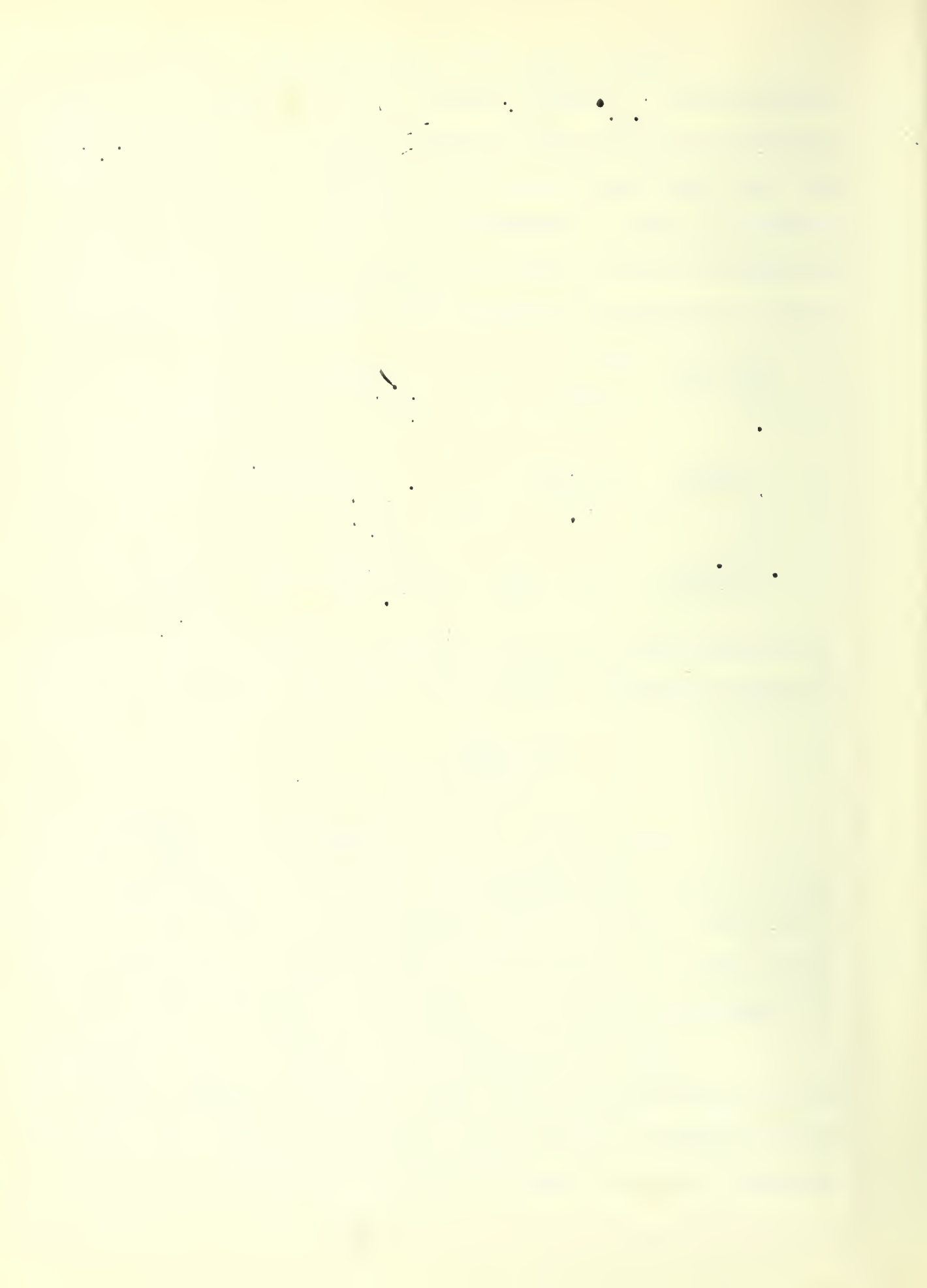


It was found that the anils separated from the reaction mixtures as hydrated compounds, and they were assigned a structure accordingly



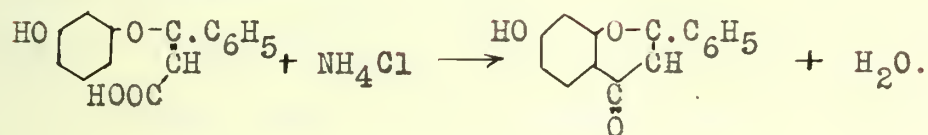
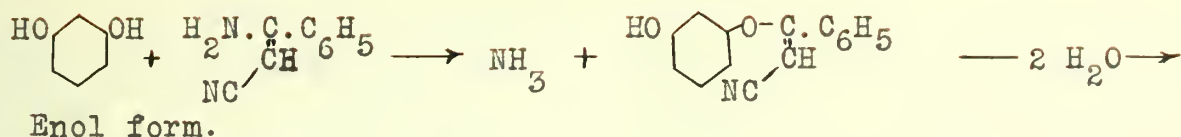
Dimroth also condensed formaldehyde aniline with pyrogallol (1-2-3-trihydroxybenzene) obtaining a 70% yield of the aldehyde, which showed that the hydroxyl groups could occur in positions other than meta to each other. This reaction was a forerunner of the Gatterman method for the synthesis of phenolic aldehydes.

Meyer<sup>(6)</sup> obtained what he believed to be 3-oxyflavone by the condensation of the imide of benzoyl acetonitrile  $\text{C}_6\text{H}_5\text{C}(\text{NH})=\text{CH}_2\text{CN}$  with resorcinol by means of dry hydrogen chloride. The mechanism proposed by him for the reaction was as follows:

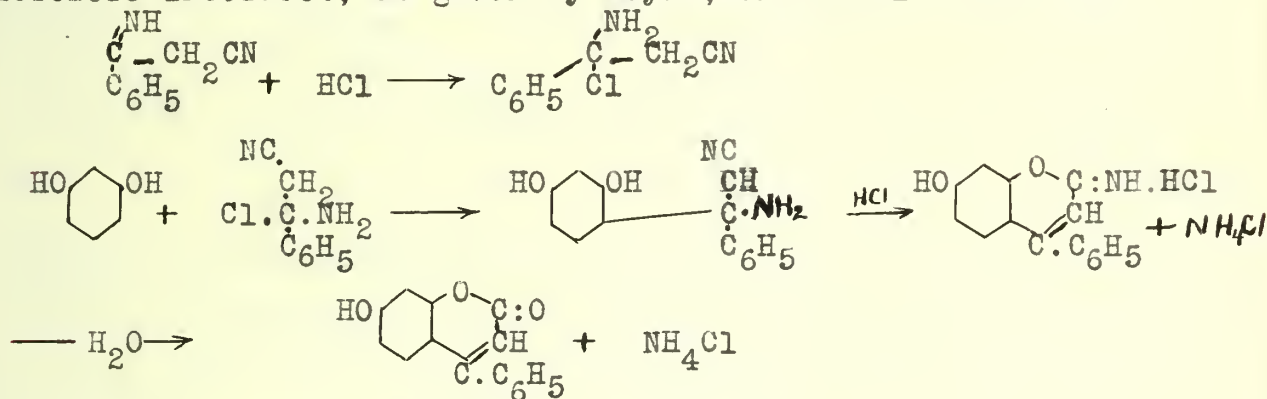




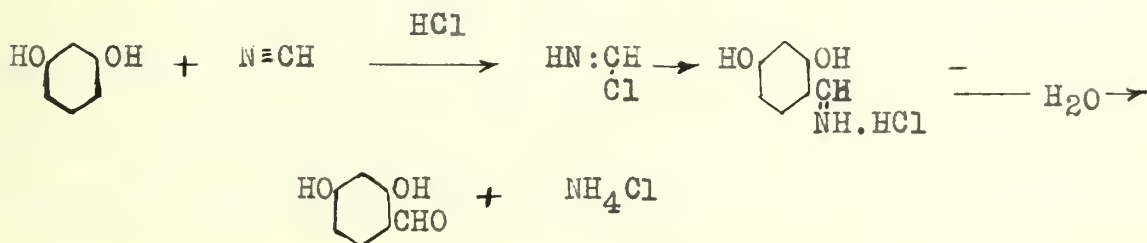
5.



Unfortunately, the details of the experiment are not given, nor definite proof of the structure of the compound obtained. Sonn later repeated the work, and proved that the compound isolated by Meyer was not a flavone, but 7-oxy  $\beta$ -phenyl coumarin. The mechanism was therefore incorrect, as given by Meyer, and should have been



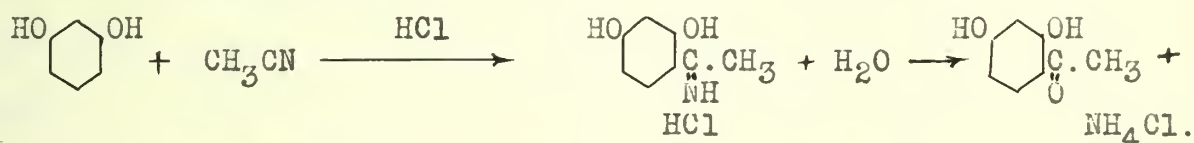
The Gatterman<sup>(7)</sup> synthesis of aldehydes by the condensation of phenols and hydrocyanic acid in dry ether solution by means of dry hydrogen chloride was discovered in 1907. The mechanism of this reaction is generally accepted as being the addition of hydrogen chloride to the nitrile, and a condensation of the chlorimide formed with the phenol. On the hydrolysis of the aldimide obtained, an aldehyde is formed.







Hoesch<sup>(8)</sup>, in seeking to extend the Gatterman aldehyde synthesis to the preparation of ketones, generalized the condensation of nitriles with phenolic compounds, and from that time the reaction, when applied to the synthesis of ketones, has been known as the Hoesch reaction. It happened that in this work nitriles were used which gave only ketones, and Hoesch proved that acetonitrile ( $\text{CH}_3\text{CN}$ ) and benzonitrile ( $\text{C}_6\text{H}_5\text{CN}$ ) could be used with dihydroxy phenols with the hydroxyl groups in the meta position to each other. The mechanism for the reactions, as given by Hoesch, is similar to that for the Gatterman aldehyde synthesis, a ketimide being formed instead of an aldimide.



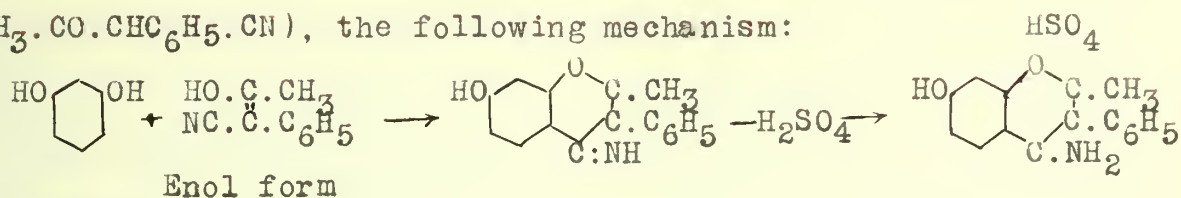
Evidence for the formation of an intermediate addition compound between hydrochloric acid and nitriles has been given by Tröger and Lüning<sup>(9)</sup>, who isolated and proved the addition product of hydrochloric acid and chloroacetonitrile ( $\text{Cl} \cdot \text{CH}_2 \cdot \text{CN}$ ) to be monochloro-acetamide chloride ( $\text{Cl} \cdot \text{CH}_2 \cdot \text{CCl} : \text{NH}$ ).

Later, Hoesch synthesized maclurin  $\begin{array}{c} \text{HO} \quad \text{OH} \\ \diagup \quad \diagdown \\ \text{C} \quad \text{C} \\ \diagdown \quad \diagup \\ \text{OH} \quad \text{O} \end{array} \begin{array}{c} \text{OH} \\ \diagup \quad \diagdown \\ \text{C}_6\text{H}_4 \\ \diagdown \quad \diagup \\ \text{OH} \end{array}$ , a product found in yellow wood, or *Morus tinctoria*, by the condensation of phloroglucinol and protocatechuic nitrile  $\begin{array}{c} \text{OH} \\ \diagup \quad \diagdown \\ \text{C}_6\text{H}_3 \\ \diagdown \quad \diagup \\ \text{CN} \end{array}$ , and also made the related compound from resorcinol and vanillic nitrile  $\text{NC} \begin{array}{c} \text{OCH}_3 \\ \diagup \quad \diagdown \\ \text{C}_6\text{H}_3 \\ \diagdown \quad \diagup \\ \text{OH} \end{array}$ .

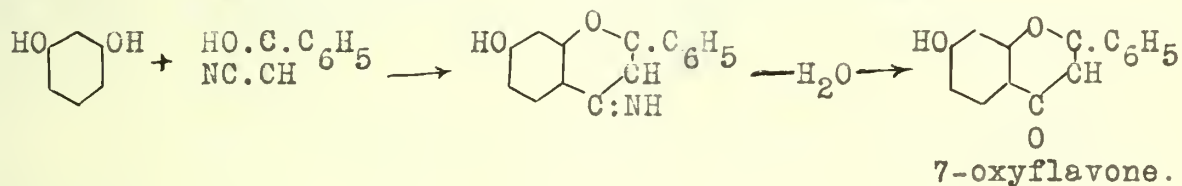
Ghosh<sup>(10)</sup> condensed benzoyl acetonitrile ( $\text{C}_6\text{H}_5\text{CO} \cdot \text{CH}_2 \cdot \text{CN}$ ) formyl acetonitrile ( $\text{OHC} \cdot \text{CH}_2 \cdot \text{CN}$ ), and other nitriles with phenols, using as condensing agents sulphuric acid, hydrochloric acid, phosphorus oxychloride, and zinc chloride. He gives, for instance,



the condensation of resorcinol and acetyl phenyl-aceto nitrile ( $\text{CH}_3.\text{CO}.\text{CHC}_6\text{H}_5.\text{CN}$ ), the following mechanism:



For the synthesis of a flavone, he used resorcinol and benzoyl acetonitrile, and explained the reaction as follows:



He proved the structure of his compounds by decomposing them with alkali and isolating the products formed, and confirms their structure by showing that they gave colored salts, and therefore must have a quinonoid structure. In view of the work done by Sonn, which proves that the mechanism given by Meyer for the condensation of the imide of benzoyl acetonitrile with resorcinol is incorrect, it must be concluded that the factor which determines the mechanism of the condensation is, as is given by Ghosh, the complexity of the substituent on the  $\alpha$  carbon atom of the esters or nitriles used, the larger groups inhibiting enolization. In confirmation of this theory, it is pointed out that ethyl acetoacetate with phenols gave only coumarins, while ethyl ethyl acetoacetate gave a mixture of the coumarins and  $\gamma$ -pyrones, and benzyl ethyl acetoacetate gave only the  $\gamma$ -pyrones.

Sonn<sup>(11)</sup> observed that the nitrile which Meyer used was readily hydrolyzed by shaking with cold mineral acids, giving benzoyl acetonitrile, and that the hydrolysis product corresponded



to the nitriles used by Bargellini and Forli-Porti<sup>(12)</sup>, in having the structure  $R.CO.CH_2.CN$ . These investigators condensed nitriles having this structure with phenols, and isolated a number of lactones and acids. The condensation depends upon the enolization of the hydrogen of the methylene group to give a compound of the type  $R.COH:CH.CN$ . Sonn used the acyl compound obtained by the hydrolysis of the imide of benzoylacetonitrile in repeating and extending the work of Meyer.

In using saturated aliphatic nitriles, Sonn was able to secure normal ketone condensation by means of the Hoesch reaction. It is important to note that he used chloracetonitrile ( $Cl.CH_2.CN$ ), and obtained a normal condensation with resorcinol,  $\omega$ -chlor-resacetophenone being isolated. This was unstable to alkali, and when an attempt was made to replace the halogen with a hydroxyl group, the ring closed to give 6-oxycumaranone. This work was done to find a method for the preparation of fisetol.

Slater and Stephen<sup>(13)</sup> also attempted to synthesize fisetol and some related compounds by means of the Hoesch reaction, using hydroxy acetonitrile and acetaldehydecyanhydrin, and while a normal ketone condensation occurred, they were unable to obtain the desired compounds due to the closure of the ring to give cumaranones. They also made similar compounds by the use of phloroglucinol in place of resorcinol. Stephen<sup>(14)</sup> later substituted cinnamanilide-imidochloride ( $C_6H_5.CH:CH.CCl:NC_6H_5$ ) and chloracetimidochloride for the nitriles, and found that neither hydrochloric acid nor zinc chloride were necessary to bring about a condensation, and that the best yields of product were obtained when the reaction mixture was





heated. This led him to advance a theory regarding the mechanism of the reaction differing from that of Hoesch. This theory involved the reaction of the halogen of the imidochloride with the hydrogen of the phenolic hydroxyl followed by a rearrangement into the ring, which rearrangement occurred best with heating. No intermediate products were isolated to which could be assigned an ether linkage.

This mechanism resembles the rearrangement of the allyl phenyl ethers to o-ally phenols, which was discovered by Claisen . Adams and Powell<sup>(16)</sup> have shown conclusively that many unsaturated groups, some of which are more reactive chemically than the allyl group, could not be rearranged into the ring upon heating for many hours. Therefore it is unreasonable to expect that the mechanism of the Hoesch reaction, which is applicable to a great number of phenols and nitriles can be explained in this way.

Fischer and Mouri<sup>(18)</sup> condensed cinnamic nitrile ( $C_6H_5 \cdot CH:CH \cdot CN$ ) and p-hydroxycoumaric nitrile  $HO \text{---} \text{C}_6\text{H}_4 \text{---} CH:CH \cdot CN$  with phloroglucinol, and found that no ketonic condensation took place. Apparently they attempted to synthesize flavones by the Hoesch condensation, but due to the unsaturated nature of the nitriles, only lactones were obtained. They did not suggest a mechanism for the reaction other than the addition of the phenol to the double bond, and the simultaneous closing of the ring to give a lactimide. However, when they used p-hydroxy -phenylpropionitrile, in which case there was no unsaturated carbon atom in the side chain to react with the phloroglucinol, they were able to secure normal condensation, and isolated phloretin  $HO \text{---} \text{C}_6\text{H}_4 \text{---} CH_2 \cdot CH_2 \cdot CO \text{---} \text{C}_6\text{H}_4 \text{---} OH$ .

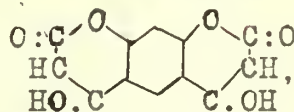
Bauer and Schoder<sup>(19)</sup> condensed cyanacetic ester with



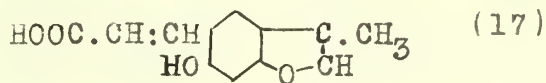


resorcinol by means of the Hoesch reaction, and obtained in this way 4-7-dioxycoumarin  $\text{HO} \begin{array}{c} \text{O} \\ \diagup \quad \diagdown \\ \text{C} \text{---} \text{C} \text{---} \text{O} \\ \diagdown \quad \diagup \\ \text{CH} \\ \text{C} \text{---} \text{OH} \end{array}$ . It is significant that they

also obtained the compound having the structure



for Karrer found that the compound of the structure

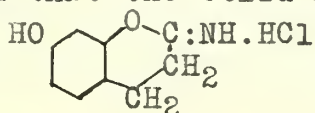


could not be made to close into the lactone, or coumarin derivative.

### III. THEORETICAL.

It has been found that  $\beta$ -chlorpropionitrile,  $\gamma$ -chlorbutyronitrile, and acrylic nitrile all condense with phenols to give nitriles, or intermediates which upon hydrolysis give lactones or acids, and that in no case is a ketone formed. Ethylene cyanhydrin has been shown not to condense at all with phenols, except to give a small amount of 2-4-dioxy  $\beta$ -phenylpropionic acid, the formation of which is undoubtedly due to the replacement of the hydroxyl of the nitrile by chlorine from hydrochloric acid, and the reaction of the resulting chlorpropionitrile with the phenol

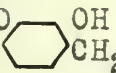
In the case of resorcinol and  $\beta$ -chlorpropionitrile, a solid intermediate product was obtained, which was a hydrochloride of a nitrogen containing compound. While the halogen analysis did not lead to a definite formula for this substance, on treatment with water, the nitrogen and halogen were instantly removed, and there was obtained the lactone of 2-4-dioxy  $\beta$ -phenyl propionic acid. This leads to the conclusion that the solid had the structure





Were it of another structure, the hydrolysis to the lactone would take much longer, for the reaction of nitriles and amides with water is comparatively slow. It could not have the structure of an open chain propionic acid derivative, for then the ring could not have closed on treatment with water to give the lactone obtained. However the isolation of this compound does not prove whether it was the  $\beta$ -halogen atom or the halogen of the chlorimide that reacted first.

The fact that acrylic nitrile gave the same lactone as  $\beta$ -chlorpropionitrile shows that it adds hydrochloric acid to give  $\beta$ -chlorpropionitrile, and that this compound condenses with the phenol. The addition of hydrobromic acid to acrylic nitrile has been shown by Moureu<sup>(20)</sup> to be practically instantaneous, and this is the only way that the saturated, halogen free lactone which is obtained can be explained. This mechanism also explains the abnormal behaviour of the compounds condensed by Fischer and Nouri. It has been shown by these workers that p-hydroxyphenyl propionitrile, which does not permit of a halogen replacing a hydrogen of the propionic residue, condenses normally with phloroglucinol.

The isolation of 2-oxy-4-methoxy  $\beta$ -phenyl propionitrile  $\text{CH}_3\text{O}$    $\text{CH}_2.\text{CH}_2.\text{CN}$  by the condensation of resorcinol monomethyl ether with  $\beta$ -chlorpropionitrile is proof of the hypothesis that it is the chlorine attached to the  $\beta$ -carbon atom that condenses first with the phenol, and that it condenses in a position ortho to a phenolic hydroxyl group. Other nitrogen compounds have been obtained as intermediates, especially in the case of  $\gamma$ -chlorbutyro nitrile, which intermediate hydrolyzed slowly on treatment with water, in marked contrast to the rapid hydrolysis of the hydrochloride of the imide obtained with resorcinol.



It has been shown that a small amount of water prevents the Hoesch condensation from taking place. This was clearly shown in an attempt to condense 2-4-dioxy  $\beta$ -phenyl propionic acid with  $\beta$ -chlorpropionitrile, when a mixture of the original acid and of its lactone were obtained, but no trace of a condensation product. It was also shown when an attempt was made to condense phloroglucinol containing water of crystallization with  $\beta$ -chlorpropionitrile when a viscous, brown, heavy liquid was isolated instead of the crystalline lactone or acid. While this liquid possessed some of the properties of a lactone, it could not be purified. It is probable that in this case the zinc chloride removed enough of the water of hydration to enable a portion of the products to condense, but that other impurities which formed prevented the isolation of the desired compounds.

It has been proved that although the halogen atom of the  $\beta$  or  $\gamma$  chlornitriles react abnormally in the Hoesch condensation, halogens in compounds other than nitriles do not react at all. It is probable that the nitrile group activates the halogen atom sufficiently to bring about the condensation, whereas in the case of other compounds, such as trimethylene bromide, or ethylene dibromide, the halogen is too inactive to condense. While it might be expected that the halogen in  $\beta$ -chlorpropionitrile is less reactive than in  $\beta$ -chlorpropionic ester, the failure of the latter to condense is probably due to a splitting of the ester by the zinc chloride and hydrochloric acid, with the formation of enough of side products to inhibit the reaction. Likewise, it might be expected that since ethylene cyanhydrin did not react because of the presence of the free hydroxyl group, the acetate of ethylene cyan-

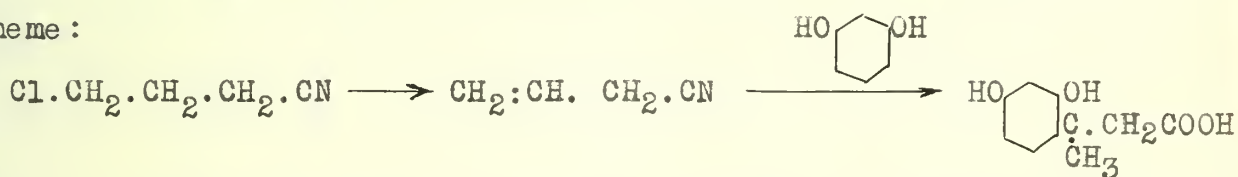




hydrin would react, But the acetate also failed to condense.

Furthermore, it has been shown that condensation of halogen substituted nitriles does not occur with phenol.

It might be supposed that in the case of the halogen substituted nitriles, hydrochloric acid first split out, leaving an unsaturated nitrile which would condense with, or add to the phenol. But three reasons militate against this hypothesis. First; acrylic nitrile does not condense with phenols until hydrochloric acid is passed into the solution. If the unsaturated nitrile were the reactive reagent, hydrochloric acid should be unnecessary for the condensation. Second; the halogen of  $\beta$ -chlorpropionitrile is not so unstable that it would split out in the presence of a saturated ethereal solution of hydrochloric acid to give an unsaturated nitrile. The ready addition of hydrobromic acid to acrylic nitrile substantiates this reason. Third; in the case of the condensation of  $\gamma$ -chlorbutyronitrile, it might be expected that instead of the  $\gamma$ -substituted acid, a  $\beta$ -substituted acid would result, as in the scheme:



The acid formed would then in all probability give a lactone as readily as 2-4-dioxy $\beta$ -phenylpropionic acid. But the acid obtained does not form a lactone on heating, and the intermediate obtained in the condensation is not in the form of a lactone imide hydrochloride, since it is fairly stable to water, and does not give a lactone on hydrolysis.

The difference in the behaviour of  $\beta$ -chlor, and  $\gamma$ -chlor nitriles from chloracetonitrile in their condensation with phenols





by means of the Hoesch reaction is attributed to the peculiar reactivity of the  $\beta$  and  $\gamma$  halogen atoms. In the same sense, the reactivity of the hydroxyl group in ethylene cyanhydrin, or the ease with which it is eliminated in the form of water explains the failure of that nitrile to react with phenols, whereas the acetaldehyde cyanhydrin reacted to give a normal condensation.

Resorcinol monomethyl ether reacts with nitriles very much more slowly than resorcinol itself, but there is little difference in the rate of reaction of resorcinol, orcinol, and phloroglucinol. It has been shown that hydrogen chloride adds on to the nitrile group comparatively slowly, for in the case of the resorcinol monomethyl ether, the nitrile was obtained from an ether solution which had been saturated for several days with hydrogen chloride. Had hydrogen chloride added to the nitrile group, there is no reason to suppose that the ring would not have closed to give a lactimide just as occurred in the condensation of resorcinol itself. The lactimide that was formed in the reaction was thrown out of the ether in the form of an oil or mixture of oil and crystals, and upon hydrolysis gave a mixture of the lactone and acid.



## IV. EXPERIMENTAL.

## A. PREPARATION OF NITRILES.

## 1. Preparation of ethylene cyanhydrin.

1285 grams of ethylene chlorhydrin were dissolved in 2 liters of 95% alcohol and heated to boiling in a 5-l. round bottom flask under an efficient reflux condenser. The flask was maintained at boiling temperature while there was added through a dropping funnel a saturated solution of 785 grams of sodium cyanide in water, the addition requiring 1 1/2 hours. A more rapid addition of the sodium cyanide was found to cause vigorous boiling, so that the reaction could not be controlled. The mixture was refluxed for twenty hours, during which time a heavy precipitate of sodium chloride was formed. The alcohol was then distilled off at atmospheric pressure, and the water distilled under 25-30 mm., the sodium chloride which separated being filtered off when bumping became too great. When all the water had been removed, the temperature rose rapidly. The last 200 cc. of water, which boiled higher than the main portion was saved separately, and fractionated once. About 20 g. of ethylene cyanhydrin was thus recovered and added to the main portion. The ethylene cyanhydrin was then distilled, the fraction boiling from 117-120° at 20 mm. being collected. The yield was 755 g. or 66% of the theory. Boiling point at atmospheric pressure was 220°.

2. Preparation of  $\beta$ -chlorpropionitrile.

In a dry liter Claisen flask were placed 450 g. of



powdered c.p. phosphorus pentachloride. Over it were poured 200 cc. of dry toluene. A thermometer was then placed in position, and over the side arm of the flask was placed an ordinary distilling flask, so that air could be drawn through it at atmospheric pressure, to carry away fumes of hydrochloric acid. The flask was cooled in an ice bath, while 145 g. of ethylene cyanhydrin were added through a dropping funnel. The addition was at such a rate that no phosphorus oxychloride distilled over, and took 1 1/2 hours. The mixture was stirred frequently during the addition, care being taken that there was no accumulation of the cyanhydrin in the toluene, for a sudden reaction would then be likely to occur, accompanied by boiling and frothing, which would cause a violent evolution of hydrogen chloride, with consequent loss of product. When all the ethylene cyanhydrin was added, the flask was connected to a low vacuum (25-30 mm.) with a water trap between the flask and the pump to catch fumes of hydrogen chloride which came off at the beginning of the distillation. The mixture of toluene and phosphorus oxychloride was distilled off on a water bath. This heating, besides removing these substances, brought the reaction to completion. When most of the toluene and phosphorus oxychloride were removed, the temperature rose slowly, the fraction coming over between 50-65° at 20mm. being collected separately and redistilled. The lower boiling portion was discarded, and the fraction which came over between 65-72° was combined with the main portion of nitrile and distilled with it. The fraction which boiled from 65-72° was fairly free of phosphorus oxychloride, and was poured carefully into about 200 cc. of water, so that the mixture did





not become warm due to the decomposition of the phosphorus oxy-chloride present. If the mixture were allowed to heat up, a considerable portion of the nitrile would become hydrolyzed and lost. The nitrile was separated from the water, washed with a solution of sodium carbonate, again with water, dried over anhydrous sodium sulfate, filtered, and distilled. It boiled between  $68-70^{\circ}$  at 20 mm., and the yield was 105-115 g. or 57-62% of the theory.

### 3. Preparation of acrylic nitrile. (20)

An intimate mixture of 90 g. of phosphorus pentoxide and 100 g. of sand was poured into a dry liter Claisen flask. Over the side arm of the flask was placed an ordinary distilling flask as a receiver, and a thermometer was placed in position. There were dropped upon the phosphorus pentoxide sand mixture 25 g. of ethylene cyanhydrin in three portions, the flask being vigorously shaken after each addition, to thoroughly mix the contents. If a thorough mixing were not obtained, a large portion of the phosphorus pentoxide would have remained unreacted upon in the bottom of the flask. The mixture was then heated either with a free flame or an oil bath at  $250^{\circ}$ , the receiver being well cooled. About 5 g. of nitrile distilled over between  $60-80^{\circ}$ . This was removed, and the receiver replaced. There was then applied a low vacuum, which was built up gradually so that the nitrile which distilled did not pass through the receiver uncondensed. Two or three more grams of nitrile were thus obtained. The nitrile was distilled once before use, and boiled between  $74-78^{\circ}$ , at atmospheric pressure, most of it coming over at  $78^{\circ}$ . The yield was 7 g. or 37% of the theory.





4. Preparation of  $\gamma$ -chlorbutyronitrile. (21)

In a 5 l. round bottom flask were placed 920 g. of trimethylene chlorbromide and 2 l. of 95% alcohol. The flask was fitted to an efficient reflux condenser, and its contents heated to boiling. There was then dropped into the mixture 285 g. of sodium cyanide dissolved in 400 cc. of water, the addition requiring about 1 hour. The reaction started almost immediately, as was shown by a darkening of the solution, and the separation of a precipitate of sodium bromide. The solution was refluxed for 1 1/2 hours, and the alcohol then distilled off directly. When the residue became thick and no more alcohol distilled at the heat of the steam cone, the distillation was discontinued. The alcoholic distillate contained practically all of the unchanged trimethylene chlorbromide, which could be recovered by diluting with water and separating the layer of chlorbromide. In this manner 50-70 g. of unchanged material were recovered.

About 1 1/2 l. of water were then added to the residue in the flask, and the layer of nitrile separated. This was dried over anhydrous sodium sulfate and filtered. The water was extracted twice with benzene, one liter being used for each extraction. The benzene was dried over anhydrous sodium sulfate, filtered, and distilled. The nitrile which remained behind was combined with the dried fraction above, and distilled. Fraction 98-102°, 146 g. Fraction 102-108°, 31 g. at 35 mm. pressure. The product was redistilled, and the fraction from 89° to 91° at 15 mm. collected. The yield was 170 g., which is 17.7% of the theory.

There was obtained in the higher boiling fraction 70 g. of trimethylene cyanide.



## B. CONDENSATIONS OF NITRILES WITH RESORCINOL.

## 1. An attempt to condense ethylene cyanhydrin with resorcinol.

Seventy one grams of ethylene cyanhydrin and 110 g. of resorcinol were dissolved in 400 cc. of dry ether, and 30 g. of powdered zinc chloride were added. Dry hydrogen chloride was then passed in until the ether was saturated. The solution became red immediately, the depth of color increasing steadily as the solution became more and more saturated. At the end of about fifteen minutes a turbidity became apparent, and shortly afterwards a liquid layer separated. The flask was allowed to stand for one day, and then more hydrogen chloride was passed in. After another day, the deposit had become viscous, red, and gummy. The ether was decanted, and the gum washed with 250 cc. of fresh dry ether. It was then treated with 300 cc. of water, and warmed on a steam bath for one hour. A clear solution resulted.

The water solution was made alkaline to sodium carbonate, and extracted three times with ether, two liters being used. The ether was dried over sodium sulfate, filtered, and distilled. There remained 42 g. of a brown oil.

In order to identify this oil, a portion was boiled in an alkaline solution with benzoyl chloride in excess. A white oil separated from the alkaline solution, which oil solidified on cooling. It was filtered off, washed thoroughly with alkali, and then with water. It crystallized out of 95% alcohol in colorless plates, and melted at  $107-114^{\circ}$ . When mixed with resorcinol dibenzoate (m.p.  $117^{\circ}$ ) it melted from  $112.5-117.5^{\circ}$ . Therefore no condensation had occurred.





The alkaline water solution was acidified, and the water evaporated under vacuum. When it had become concentrated, the solution was allowed to stand, when four grams of hard nuclear crystals of 2-4-dihydroxy  $\beta$ -phenylpropionic acid separated.

To determine whether or not the zinc chloride had had a dehydrating action upon the ethylene cyanhydrin and prevented the condensation, the above was repeated, the zinc chloride being omitted. Practically identical results were obtained.

The condensations of ethylene cyanhydrin with resorcinol mono-and di-methyl ethers were also tried, but in no case could a condensation product be isolated.

2. An attempt to condense  $\beta$ -cyanethyl-acetate with resorcinol.

In a 500 cc. flask were dissolved together 47 g. of  $\beta$ -cyanethyl-acetate, 45 g. of resorcinol, 250 cc. of dry ether, and 15 g. of powdered zinc chloride. Dry hydrogen chloride was then passed into the mixture until it was saturated. At the end of 1/2 hour, a turbidity resulted, which was soon followed by the separation of a viscous liquid on the bottom of the flask. After twelve hours standing, more hydrogen chloride was passed in, and the flask sealed for several more hours. The ether was decanted, and the residue treated with 100 cc. of water. The product dissolved completely. The flask was heated for 2 hours on a steam bath, and cooled, but no product separated. The solution was extracted twice with 250 cc. portions of ether, the ether dried over anhydrous sodium sulfate, filtered, and distilled. A small amount of oil remained, but it could not be purified.





The ether layer from the reaction mixture was evaporated, and the residue distilled under vacuum. There were recovered 36 g. of resorcinol, melting at 95-106°. Mixed with resorcinol it melted from 103-109°. The reaction mixture was therefore discarded.

### 3. Condensation of $\beta$ -chlorpropionitrile with resorcinol.

In a 2 l. flask was placed 130 g. of pure resorcinol, 90 g. of  $\beta$ -chlorpropionitrile, and 700 cc. of dry ether. Forty grams of zinc chloride were fused, powdered, and added to the ether solution. Dry hydrogen chloride was then passed into the ether as long as it was absorbed, and then the flask was sealed and allowed to stand overnight. Dry hydrogen chloride was again slowly passed in for a period of five hours, and the flask allowed to stand 36 hours longer. The mass of crystals which separated were then filtered with suction, and washed with dry ether. The ether was allowed to stand and after 2 more days, 38 g. more of solid had formed. On standing a week more, 25 additional grams of crystals were obtained.

The solid was dissolved in 450 cc. of water, and heated on a steam bath for four hours. An oil layer first separated, and then went into solution as the heating was continued. The solution was then cooled, and allowed to stand overnight, when 86.5 g. of 2-4-dihydroxy  $\beta$ -phenylpropionic acid were filtered off. The aqueous filtrate was evaporated under vacuum to about 175 cc. and allowed to stand, when a second crop of crystals, weighing 22.5 g. was obtained. On further concentration of the filtrate, only inorganic salts separated out. Total yield, 109 g. or 56% of the theory.



Analysis: Subst. .3679 g.	CO <sub>2</sub> .7962 g.	H <sub>2</sub> O . 1799 g.
Cal. C <sub>9</sub> H <sub>10</sub> O <sub>4</sub>	C 59.34%	H 5.49%
Found	C 59.05%	H 5.49%

2-4-dioxy  $\beta$ -phenylpropionic acid, as it was obtained, was light brown, and did not lose its color even when boiled with bone black. When prepared from its pure lactone, it may be obtained perfectly colorless. The crystals are hard, shiny nodules, and melt at 165° with decomposition. The acid crystallizes out of water slowly, is insoluble in benzene, toluene, chloroform, and ligroin, difficulty soluble in ether, very soluble in methyl, ethyl, isopropyl, and butyl alcohols, acetone, and ethyl acetate. It decomposes sodium carbonate very readily in the cold.

A portion of the solid, when melted in a 2" test tube, showed no signs of decomposition until the melting point was reached, when bubbles permeated the clear light brown liquid, and moisture collected in the upper portions of the tube. The liquid recrystallized on standing, and then melted at 124-128°.

It was found, however, that hydroumbellic acid, as this acid is called, when heated above 125° for a period of 2 hours, melted down to a dark red mass, which lost 24% by weight instead of the 9.39%, which is the theoretical loss in weight upon the formation of the lactone.

Neutral equivalent of 2-4-dihydroxy  $\beta$ -phenylpropionic acid.

Subst. .2973 g. NaOH (.0717 N.) 24.94 cc.

Neutral equivalent calculated 182, found 171.

2-4-dioxy  $\beta$ -phenyl propionic acid was prepared by Hlasiwetz by the reduction of umbelliferone,<sup>(22)</sup> but the constants



given by him are found to differ from the constants of a pure sample. Hlasiwetz states that the acid decomposes when heated above  $110^{\circ}$ , whereas a pure sample melts at  $165^{\circ}$  if not heated too slowly. Upon very slow heating, enough of the lactone is formed to cause a lowering of the melting point. Hlasiwetz isolated a compound which analyzed for the lactone of hydroumbellic acid, but as he was unable to purify it, did not identify it, nor give constants for it.

#### Isolation of the intermediate imide-hydrochloride.

Five grams of resorcinol and 5 g. of  $\beta$ -chlorpropionitrile were dissolved in 50 cc. of dry ether, and hydrogen chloride was passed in until the ether was saturated. The flask was then sealed and allowed to stand. After 12 hours a small amount of precipitate had formed, but the flask was allowed to stand for a week before the ether was filtered. There were thus isolated 2.5 g. of colorless solid. The crude product decomposed from  $178-180^{\circ}$ . On being dried, it became sticky, and it was washed with absolute alcohol saturated with hydrogen chloride, and then with acetone. The product was then dried in air until the odor of acetone and of hydrochloric acid was gone.

Analysis: Chlorine, by peroxide fusion method.

1. Subst.	.2778 g.	$\text{AgNO}_3$ (.1050 N.)	17.72 cc.
Cal.	$\text{C}_9\text{H}_{10}\text{O}_2\text{NCl}$	Cl 18%.	Found Cl 23.72%.
2. Subst.	.5020 g.	$\text{AgNO}_3$	32.55 cc.
			Found Cl 24.11%

A portion of this compound, when treated with water, was instantly converted into an oil, which solidified on cooling.





This new compound crystallized readily from toluene, and was shown to be 7-hydroxy chromanone-2, or the lactone of 2-4-dihydroxy  $\beta$ -phenylpropionic acid.

#### Preparation of 7-hydroxy chromanone-2.

Two grams of 2-4-dihydroxy  $\beta$ -phenyl propionic acid were heated in an oven at 130-135° for two hours. The melt was allowed to cool, and then was crystallized from toluene. A white solid resulted, melting at 130-132°. On recrystallization, it melted at 132-133°.

Analysis:	Subst.	.1560 g.	CO <sub>2</sub>	.3795 g.	H <sub>2</sub> O	.0072 g.
	Calculated	C <sub>9</sub> H <sub>8</sub> O <sub>3</sub>	C	65.85%	H	4.88%
	Found		C	66.33%	H	4.96%

7-hydroxy chromanone-2 separated from solution in colorless cubical crystals. It was very soluble in methyl, ethyl, and butyl alcohols, acetone, and acetic acid; insoluble in benzene, water, ligroin, chloroform, and carbon tetrachloride. It was insoluble in sodium carbonate until the solution was heated, when it went into solution, and did not come out again until the solution was acidified and allowed to stand for some time. It then deposited in the form of hard crystals of 2-4-dihydroxy  $\beta$ -phenyl propionic acid. It gave no coloration with ferric chloride on warming, but when the solution was allowed to stand for some time, a brown coloration developed.

This lactone did not react with butyl nitrite to give a nitroso derivative under the same conditions as <sup>old</sup> 2-4-dihydroxy  $\beta$ -phenylpropionic acid.





## Preparation of the acetate of 7-hydroxy-chromanone-2.

Seven grams of 2-4-dihydroxy  $\beta$ -phenylpropionic acid were dissolved in 10 g. of acetic anhydride (2 mols.) and heated on a water bath for one hour. The solution developed a light red color. The mixture was cooled, and poured into 70 cc. of cold water, whereupon a yellow crystalline substance was thrown out. It melted at  $100.5-108^{\circ}$  when unpurified. The yield was 9 g., which was practically quantitative. It was recrystallized twice from 20% methyl alcohol, after which it melted at  $111-112^{\circ}$ .

Analysis:	Subst.	.3116 g.	CO <sub>2</sub>	.7382 g.	H <sub>2</sub> O	.1357 g.
	Cal.	C <sub>11</sub> H <sub>10</sub> O <sub>4</sub> ,	C	64.1%	H	4.67%
	Found		C	64.63	H	4.83

The acetate was in the form of colorless needles, insoluble in sodium carbonate until heated, when it decomposed. It hydrolyzed readily when boiled with water, giving 2-4-dihydroxy  $\beta$ -phenylpropionic acid.

Preparation of 2-4-dimethoxy  $\beta$ -phenylpropionic acid.

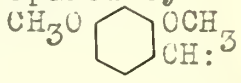
In 100 cc. of 10% sodium hydroxide were dissolved 35 g. of 2-4-dihydroxy  $\beta$ -phenylpropionic acid, and 36 g. of dimethyl sulfate were added. The solution was thoroughly shaken, and then warmed on a steam bath under a reflux condenser. A reaction took place, in which heat was evolved, and the dimethyl sulfate passed into solution. There were then added another 100 cc. of 10% sodium hydroxide and 35 g. of dimethyl sulfate, and the mixture again heated until all of the dimethyl sulfate was decomposed. The solution was then cooled, acidified, and stirred, when needle crystals separated. After standing for about an hour, the solution was



filtered, and the precipitate dried. The compound melted at 98-103°, and the yield was 28.5 g. or 68% of the theory.

A portion of the compound was recrystallized from water, in which it was difficulty soluble, and it then melted at 102-103°. On a second recrystallization, it melted at 102.5-103.5°.

Analysis:-	Subst. .1260 g.	CO <sub>2</sub> .6896 g.	H <sub>2</sub> O .1739
	Cal. C <sub>11</sub> H <sub>14</sub> O <sub>4</sub>	C 62.8%	H 6.6%
	Found	C 62.87%	H 6 6.5%

This was therefore beyond doubt the acid prepared by W. Will<sup>(23)</sup>, by the reduction of dimethoxy umbellic acid  CH<sub>3</sub>COOH. The melting point given by him was 105°.

#### Neutralization equivalent

Subst. .1260 g.	NaOH (.0717 N.) 8.74 cc.
Cal. N.E. 210	Found 201.

#### Preparation of 6-nitroso-7-hydroxy chromanone-2.

In 50 cc. of 95% alcohol were dissolved 3 g. of 2-4-dihydroxy *β*-phenylpropionic acid, and to the solution were added 4 g. of butyl nitrite, which had been freshly distilled, and boiled at 78°. The flask was then cooled under running water, and 10 cc. of concentrated hydrochloric acid added. Fumes of nitric oxide were evolved, heat was generated, and a red precipitate formed. 40 cc. more of concentrated hydrochloric acid were then added, and the flask allowed to stand for twenty to thirty minutes. The solid was then filtered off, washed twice with cold water, and dried. The yield was 4 grams, or practically quantitative. The washed compound was of a light cream color, but on exposure to air, it



turned green. In other preparations, the solid came out as a red precipitate from which the color was difficult to remove, even when boiled with bone-black.

Four grams were dissolved in 70 cc. of boiling water, and filtered hot. The aqueous solution turned very green, but the product separated out cream colored. It was filtered off, and placed in a dessicator over sulfuric acid, in which it did not discolor on standing. The weight of the dried product was 2.5 g. and it melted at 147.5-148°.

Analysis: Nitrogen by Dumas method.

Subst. .1873 g. N collected 13.1 cc. at 26° and  
737.3 mm.

Cal.  $C_9H_7O_4$  N 7.25% Found 7.61%

6-nitroso 7-hydroxy chromanone-2 is an amorphous powder, which slowly turned dark brown at 110°. It was difficulty soluble in cold alcohol, but readily soluble hot. When once dissolved, it did not come out again on cooling. It was practically insoluble in cold water, and decomposed sodium carbonate, acting as a monobasic acid, although due to coloration of the solution when alkali was added, no quantitative titration could be obtained.

To prove that the nitroso group was in the benzene portion of the molecule and not in the pyrone ring, an attempt was made to hydrolyze it.

Twenty grams of 6-nitroso 7-hydroxy chromanone-2 were treated with 80 cc. of water and 20 g. of concentrated sulphuric acid. The flask was connected to an air condenser, and a tube connected from the top of the condenser to a flask containing a solution of barium hydroxide. The flask was then heated on a steam





bath. Almost immediately a gas was evolved, and a precipitate formed in the barium hydroxide. This precipitate was readily soluble in acids with effervescence, carbon dioxide being evolved.

After four hours of heating, the reaction mixture was cooled, and extracted four times with ether, 1 1/2 l. being used. There were about 2 g. of carbon left in suspension in the water. The ether was dried over anhydrous sodium sulfate, filtered, and distilled. A brown, viscous liquid remained. It decomposed sodium carbonate readily in the cold, and reacted acid to litmus, which showed it to be an organic acid. It was placed in a dessicator, and allowed to stand for nearly a month, but failed to crystallize. Numerous attempts were made to prepare a derivative of this acid, but all were unsuccessful.

After the ether extraction, the sulfuric acid solution was made alkaline with excess of sodium hydroxide and boiled with 15 g. of benzoyl chloride. On cooling the solution, a solid separated from the alkaline reaction mixture. This was filtered off, washed with dilute alkali, and then with water. The solid was in the form of cream colored needles, 6 g. being obtained. It crystallized out of water, and melted at 124.5-125.5°. Mixed with benzamide, it melted at 124.5-126.5°.

The formation of carbon dioxide and ammonia upon the hydrolysis of the nitroso compound, and the formation of a liquid acid which could not be purified point to a deep seated change in the molecule. No trace of aldehyde could be detected either in the gas evolved, in the acid extracted by the ether, or in the sulphuric acid residue. Were the nitroso group in the aliphatic portion of the molecule, there seems little doubt but that 2-4- $\beta$



dihydroxyphenyl acetaldehyde could have been isolated, or at least detected. It was therefore concluded that the nitroso group was in the benzene ring.

#### Preparation of umbelliferone. (24)

In a 500 cc. round bottom flask were placed 26 g. of malic acid and 23 g. of resorcinol. Over the mixture were then poured 100 g. of concentrated sulphuric acid, and the flask was stirred until complete solution had resulted. The flask was connected to a reflux condenser, and heat was applied with a free flame. When formic acid began to be evolved, the flame was removed, and the flask was shaken vigorously. In a short time the reaction mixture solidified to a cream colored product. After this first reaction had ceased, the flask was heated gently, with occasional stirring, for a period of three hours, during which time the solid gradually dissolved. The entire mixture was then poured into 2 l. of ice and water, and allowed to stand for five or six hours. A red precipitate of umbelliferone separated. The solution was filtered, and the precipitate washed thoroughly with water, and dried. The yield was 9 g.

A portion of the product was recrystallized from water, bone-black being added to remove some of the color. Orange crystals melting at  $222.5-225^{\circ}$  were obtained. The melting point of umbelliferone is  $223-224^{\circ}$ .

#### Reduction of umbelliferone.

(Preparation of 2-4-dihydroxy  $\beta$ -phenylpropionic acid)

2.4 g. of umbelliferone were dissolved in 12 cc. of



10% sodium hydroxide, a red coloration resulting. To prevent the solution from becoming too concentrated, 10 cc. of water were then added. Sodium amalgam was dropped into the flask in small amounts until the red color had disappeared, about 1 hour being required. The solution was acidified with hydrochloric acid, filtered, and allowed to stand. Red crystals deposited. They decomposed at 149-157°, and when mixed with 2-4-dihydroxy *β*-phenylpropionic acid, melted with decomposition at 155-159°. The yield was .6 gram.

#### Preparation of acetate of 7-hydroxy chromanone-2.

Into 5 cc. of acetic anhydride were placed .5 g. of the 2-4-dihydroxy *β*-phenylpropionic acid from umbelliferone, and the solution was heated for 20 minutes. The contents of the flask were then poured into 20 cc. of water, and stirred until the excess of acetic anhydride was decomposed. A brown solid remained. This was filtered, washed thoroughly with water, and crystallized from 30 cc. of 20% methyl alcohol. It came out as a white powder, melting at 109-112°. Mixed with the acetate prepared from resorcinol and *β*-chlorpropionitrile, it melted at 112-112.5°. The products were therefore identical.

#### 4. Condensation of acrylic nitrile with resorcinol.

Twelve grams of resorcinol and 6 g. of acrylic nitrile were dissolved in 70 cc. of dry ether, and 4 g. of powdered zinc chloride added. Dry hydrogen chloride was then passed in until the ether was saturated, and the flask was allowed to stand for twelve hours. At the end of that time, a heavy white crystalline product had separated. The ether was decanted, and a small portion of the





solid was removed and treated with water. It immediately became an oil, and when it was cooled, solidified. It crystallized from toluene, and melted at  $132.5-134^{\circ}$ . Mixed with 7-hydroxy chromanone -2, it melted at  $133-134^{\circ}$ .

The remainder of the solid was boiled with 50 cc. of water for 1/2 hour, and then allowed to stand. Crystals separated, which melted with decomposition at  $152-158^{\circ}$ . The mixed melting point with 2-4-dihydroxy  $\beta$ -phenylpropionic acid was  $155-158^{\circ}$ . The yield was 4 g. or 20% of the theory.

#### 5. Condensation of $\gamma$ -chlorbutyronitrile with resorcinol.

Sixty four grams of resorcinol and 60 g. of  $\gamma$ -chlorbutyronitrile were dissolved in 400 cc. of dry ether, and 30 g. of powdered zinc chloride added. Dry hydrogen chloride was then passed in in a rapid stream for two hours. The solution turned red, and a small amount of liquid separated. For two successive days, for an hour each day, hydrogen chloride was passed in, the amount of liquid deposited increasing slowly during this time. After six days, the liquid layer which had formed had entirely crystallized.

The ether was filtered, and the residue taken up in 250 cc. of water. It was heated for three hours on the steam bath. An oil layer separated at first, and went into solution as heating was continued. On standing, crystals formed. They were filtered, and dried. Yield, 24.5 g. or 20.8% of the theory.

Ten grams of the product were dissolved in 57 cc. of boiling water, and filtered hot. An oil separated, which on being cooled and stirred, solidified. The weight recovered was 9.5 g.,





and a portion melted at  $89-99^{\circ}$ .

2-4-dihydroxy  $\gamma$ -phenylbutyric acid is a colorless, crystalline solid, which came out of water in plates with one molecule of water of crystallization, which it lost at about  $90^{\circ}$ . After several recrystallizations from water, one sample melted from  $89^{\circ}$  to  $104.5^{\circ}$ . On standing, the melt resolidified, and remelted at  $118-119^{\circ}$ .

Moisture determination: Subst. . 7322 g. Heated at  $80^{\circ}$  for 1 1/2 hours, and then at  $95^{\circ}$  for 1 hour.  $H_2O$  lost .0655 g. Cal.-  
 $H_2O$  .0615 g.

Subst. .5297 g. Heated 1 hour at  $80-85^{\circ}$ , and 1 hour at  $100^{\circ}$ .  $H_2O$  lost .0471 g. or 8.89%. Cal. loss 8.4%

The anhydrous product was readily crystallized from benzene, and melted at  $118.5-119^{\circ}$ . It was in the form of colorless plates.

Analysis: Subst. .2560 g.	$CO_2$ .3640 g.	$H_2O$ .0865 g.
Cal. $C_{10}H_{12}O_4$	C 61.22%	H 6.12%
Found	C 60.96%	H 5.95%

Neutralization equivalent.

Subst. .1491 g. NaOH (.0717 N.) 9.98 cc.

Cal. N.E. 198 Found 208.

A portion of the anhydrous 2-4-dihydroxy  $\gamma$ -phenylbutyric acid was heated in an oven at  $133-134^{\circ}$  for 1/2 hour. The solid melted down to a red liquid. It solidified on cooling, and crystallized from dry toluene as a yellow powder, melting  $113-117^{\circ}$ . Mixed with 2-4-dihydroxy  $\gamma$ -phenyl butyric acid, it melted at  $115-118^{\circ}$ . Therefore no lactone was formed.



In order to study the intermediate products formed in the condensation of resorcinol and  $\gamma$ -chlorbutyronitrile, another condensation was run under the same conditions as are given above. The product obtained was treated with water, warmed to  $50^{\circ}$ , and then cooled. The oil which formed solidified, and the solid melted at  $214-216^{\circ}$ . When it was washed with water, the melting point dropped to  $190-192^{\circ}$ , and the compound became yellow. This could be crystallized from methyl alcohol, and when the product obtained was washed with methyl alcohol saturated with hydrogen chloride, the melting point went up to  $215-216^{\circ}$ , and the solid became white.

Analysis: Subst. .3859 g.  $\text{AgNO}_3$  (.1050 N.) 25.77 cc.

Cal.  $\text{C}_{10}\text{H}_{13}\text{O}_2\text{NCl}_2$  Cl 28.4% Found Cl 25.04%

Subst. .4489 g.  $\text{AgNO}_3$  30.42 cc.

(Parr bomb fusion) Found Cl 25.22%.

This product was washed thoroughly with dilute sodium bicarbonate, and then with water. The yellow compound obtained was then analyzed for halogen. It melted at  $193.5-194.5^{\circ}$ .

Analysis: Subst. .2623 g.  $\text{AgNO}_3$  (.1050 N.) 14.04 cc.

Cal.  $\text{C}_{10}\text{H}_{12}\text{O}_2\text{NCl}$  Cl 16.5% Found Cl 18.6%

Subst. .3382 g.  $\text{AgNO}_3$  17.86 cc.

Found Cl 19.6%

The wash waters, on acidification, gave a small amount of white solid, which proved to be 2-4-dihydroxy  $\gamma$ -phenylbutyric acid.

## C. CONDENSATIONS OF NITRILES WITH RESORCINOL MONOMETHYL ETHER.

1. Condensation of  $\beta$ -chlorpropionitrile with resorcinol monomethyl ether.



Thirty grams of resorcinol monomethyl ether and 22 g. of  $\beta$ -chlorpropionitrile were dissolved in 300 cc. of dry ether, and 20 g. of powdered zinc chloride added. The ether was cooled in an ice bath, and dry hydrogen chloride passed in until it was saturated. The flask was then allowed to stand overnight. A viscous syrupy mass had formed in the bottom of the flask. The ether was decanted, and the residue treated with 30 cc. of water. After standing overnight, a small amount of solid, and some liquid had separated. The solid was removed from the oil by filtration with suction, and when dried, weighed 3.5 g. The liquid, which weighed about 10 g. was not worked up at this time.

The ether solution was evaporated under vacuum, and the unchanged  $\beta$ -chlorpropionitrile distilled, 12 g. being recovered. Then there distilled a higher boiling fraction which proved to be unchanged resorcinol monomethyl ether, of which 21 g. were recovered. The residue in the flask did not distil, but solidified on cooling. It weighed 6 grams. A small portion was crystallized from dilute alcohol, when it melted from 118-122°. After two recrystallizations, it melted at 126-127.5°. It proved to be 2-hydroxy 4-methoxy  $\beta$ -phenylpropionitrile. It was insoluble in sodium carbonate but soluble in sodium hydroxide, being thrown out again unchanged on acidification. When boiled with alkali, it evolved ammonia, and gave on acidification, colorless crystals of 2-hydroxy 4-methoxy  $\beta$ -phenyl propionic acid.

Analysis: Nitrogen by Dumas method.

Subst. .3718 g. N collected 27.2.cc. at 28°, 749 mm.

Calculated  $C_{10}H_{11}O_2N$  N 7.9%

Found N 8.0%





The solid obtained by filtration proved to be 2-hydroxy 4-methoxy  $\beta$ -phenylpropionic acid. It was recrystallized from water, in which it was difficultly soluble, 4.5 g. dissolving in 200 cc. It came out as white kernels, melting at 138-139°.

Analysis: Subst.	.3819 g.	CO <sub>2</sub>	.8604 g.	H <sub>2</sub> O	.1982 g.
Cal. C <sub>10</sub> H <sub>12</sub> O <sub>4</sub>		C	61.2%	H	6.1%
Found		C	61.4%	H	5.8%

The acid was readily soluble in sodium bicarbonate, and was thrown out again by acids unchanged. It was very soluble in alcohol, acetone, and acetic acid. It was insoluble in cold benzene and toluene.

A gram sample of 2-hydroxy 4-methoxy  $\beta$ -phenylpropionic acid was heated in an oven at 132°. The solid melted down, and was removed at the end of 3/4 hours. There was no trace of discoloration and a thick syrup remained. This did not crystallize on standing, nor would it crystallize out of any solvents tried. The product proved to be insoluble in cold sodium hydroxide, but dissolved on warming, and on acidification, yielded the original acid.

About twenty grams of the 7-methoxy chromanone-2 were placed in a 50 cc. Claisen flask, and distillation at 6 mm. pressure was attempted. A small portion of colorless oil came over from 170-210°, but the remainder of the product carbonized in the flask. As the chemical behaviour of the liquid left no doubt as to the lactone nature of the compound, no further attempt to purify it has been made up to this time.



## D. CONDENSATION OF NITRILES WITH ORCINOL.

1. Condensation of orcinol with  $\beta$ -chlorpropionitrile.

Five grams of orcinol were dissolved with 5 g. of  $\beta$ -chlorpropionitrile in 100 cc. of dry ether, and 5 g. of powdered zinc chloride added. The ether was cooled in an ice bath, and dry hydrogen chloride passed in until the ether was saturated. The flask was then allowed to stand overnight. A white precipitate formed, and after ten hours, there seemed to be no more deposit forming. The ether was decanted, and the solid washed with dry ether. It was then treated with 20 cc. of water, warmed to  $50^{\circ}$ , and cooled immediately. An oil layer formed, but it did not crystallize, even when dissolved in hot toluene and cooled. The mixture was therefore heated on a steam cone for one hour, until the oil had completely gone into solution, and did not reappear on cooling. To make sure that the lactone was converted into the acid, ammonia was added until the solution reacted neutral to litmus, and it was boiled for several minutes with boneblack, filtered, acidified, and cooled in an ice bath for several hours. Crystals separated, and a portion melted at  $77-82^{\circ}$ . The first fraction weighed 1.3 g. The water was evaporated down about half way, and chilled again, when .9 g. more of solid separated. This solid, on recrystallization melted at  $82-84.5^{\circ}$ . It was partly soluble in sodium carbonate, and to dissolve out all the soluble portion, it was mixed with excess sodium carbonate and filtered. The insoluble portion was recrystallized from water, and it melted at  $138.5-141^{\circ}$ , .7 g. being obtained. As this was not enough to purify further, it was analyzed directly.



Analysis:	Subst.	.3923 g.	CO <sub>2</sub>	.9641 g.	H <sub>2</sub> O	.1934 g.
	Calculated	C <sub>10</sub> H <sub>10</sub> O <sub>3</sub>	C	67.4%	H	5.6%
	Found		C	67.01%	H	5.5%

The sample analyzed was contaminated so that it appeared pink, but some of the crystals, when held up to the light, were colorless.

The sodium carbonate solution was acidified with hydrochloric acid, whereupon a considerable portion of an oil separated. This was removed by filtration, and the water was allowed to stand. After 24 hours, brown, cubical crystals had formed. They melted at 140-142°. Mixed with the 5-methyl 7-hydroxy chromanone-2 which was analyzed, they melted at 140-141.5°.

Since no 2-4-dihydroxy 6-methyl *β*-phenylpropionic acid could be isolated in this reaction, it was concluded that the free acid was unstable, and closed spontaneously to give the lactone.

#### E. CONDENSATIONS OF NITRILES WITH PHLOROGLUCINOL.

##### 1. Condensation of phloroglucinol with *β*-chlorpropionitrile.

Five grams of pure phloroglucinol, which had been dried at 120° for 1 1/2 hours, and 5 g. of *β*-chlorpropionitrile were dissolved in 100 cc. of dry ether, and 4 g. of powdered zinc chloride were added. The flask was cooled with ice, and dry hydrogen chloride was passed in until the solution was saturated. A brown liquid separated in the bottom of the flask, and after standing for about one hour, it began to solidify. The flask was allowed to stand for 20 hours, when most of the liquid had solidi-





fied. The ether was decanted, and the residue washed with dry ether. It was then treated with 20 cc. of water, warmed to about 40° for 5 minutes, and then cooled. No oil layer separated. After standing for 24 hours, it was extracted twice with butyl alcohol, the butyl alcohol washed once with water, and the wash water extracted again with butyl alcohol. The water was colorless, and was discarded. The butyl alcohol was distilled off under vacuum, when about 10-12 g. of dark brown liquid remained. This was taken up in 150 cc. of boiling water, heated to boiling until all of the butyl alcohol was removed, bone-blackened, and filtered. The filtrate was light colored, and from it there separated about 5 g. of a viscous oil. This failed to crystallize on standing for one week. When it was placed in a desiccator and allowed to dry thoroughly, the oil became glassy, and could not be purified.

The oil was very soluble in sodium carbonate, and upon acidification, came out again as an oil. Numerous attempts were made to prepare derivatives of the oil, such as derivatives with phenyl isocyanate, diphenyl carbamine chloride, and the lead salt. The two former condensation products came out as oils, and the lead salt did not analyze for any definite compound. In addition, attempts were made to prepare an acetate, and a benzoate of the oil. The acetate could not be purified, and the benzoate could not be isolated, as the acid group which was present made it soluble in alkali, and upon treating the compound with boiling water to remove the benzoic acid, the derivative was saponified, and therefore could not be isolated.

In order to compare the product obtained in this condensation with that obtained from acrylic nitrile, a reaction was



run with these two substances.

## 2. Condensation of phloroglucinol with acrylic nitrile.

In 100 cc. dry ether were dissolved 4.5 g. of dry phloroglucinol, and 2.2 g. of acrylic nitrile. There were added 2 g. of powdered zinc chloride, and the ether cooled in ice, while a stream of hydrogen chloride was passed in. An instant turbidity occurred, followed by the separation of a liquid layer. On standing overnight, the liquid in the bottom of the flask had entirely solidified. The ether was decanted, the product washed with ether, and then treated with 20 cc. of water. It dissolved and did not come out again on cooling.

The water solution was extracted with butyl alcohol, and the alcohol was distilled off under vacuum. A brown glassy liquid was obtained, but it failed to crystallize. The weight of the product was estimated at 5 grams. It was boiled up with 100 cc. of water, boneblackened, filtered, and the solution chilled to zero degrees. A solid separated, and a portion of it melted at 130-132°. The yield was 1.5 g.

The solid was crystallized once from water, after which it sintered at 134-135°, and melted at 139-140°. As there was not enough of it obtained for further purification, it was analyzed.

Analysis:	Subst.	.2612 g.	CO <sub>2</sub>	.5799 g.	H <sub>2</sub> O	.1631 g.
	Cal. C <sub>9</sub> H <sub>8</sub> O <sub>4</sub>		C	60.0%	H	4.4%
	Found		C	60.5%	H	6.2%

This analysis was not accepted as a good analysis, as a certain amount of volatile copper salts blew into the sulfuric



acid, which accounts for the high result for hydrogen. However, as there was not enough of the substance at hand to be analyzed again, this reaction will have to be repeated.

### 3. Condensation of phloroglucinol with $\gamma$ -chlorbutyronitrile.

A condensation, identical with the ones already described was run with 5 g. of  $\gamma$ -chlorbutyronitrile and 5 g. of phloroglucinol. The reaction mixture was allowed to stand for six days. The residue, after the decantation of the ether, was treated with 20 cc. of water, and heated on a steam bath for three hours. The flask was cooled in ice, when a brown solid separated. It was filtered off, washed with water, and dried. The compound was stable at  $245^{\circ}$ , and was readily soluble in cold sodium carbonate. On acidification of the alkaline solution, the compound was thrown out again, although it crystallized slowly. Owing to the lack of time, an analysis of this compound has not been made to date. Yield 2.5 g.

### F. OTHER CONDENSATIONS ATTEMPTED.

Attempts were made to condense in the same manner as has been already described for nitriles, other halogen compounds with resorcinol. The principal ones tried were ethylene dibromide, trimethylene bromide, chloracetic ester,  $\beta$ -chlorpropionic ester, and allyl bromide. Only in the case of allyl bromide was any product at all obtained, and in this case, there separated .6 g. of a solid which melted from  $167-175^{\circ}$ , from 10 g. of resorcinol and 12 g. of allyl bromide. This experiment was therefore repeated, a larger amount of reagents being used, and a longer time being







allowed for the condensation, but again only a very small amount of solid was obtained. This was not worked up further.

An attempt was made to condense phenol with  $\beta$ -chlorpropionitrile, but there was no evidence of a reaction taking place. The ether solution was allowed to stand for twenty four hours, and the ether was removed by distillation. Out of 10 g. of  $\beta$ -chlorpropionitrile used there were recovered 9 g. unchanged.

In an identical manner, a condensation between 2-4-dihydroxy  $\beta$ -phenylpropionic acid and  $\beta$ -chlorpropionitrile was tried. There was recovered from the reaction mixture a large proportion of the acid unchanged, and in addition, some of the corresponding lactone, or 7-hydroxy chromanone-2.

## V.

## SUMMARY.

The reaction of certain nitriles with phenols has been studied, and found to be unlike the reactions secured by Hoesch. Instead of ketones, there have been isolated nitriles, lactones, and acids.

The reaction of nitriles with phenols under the conditions studied has been shown to be limited to compounds from which water can not be readily eliminated.

It has been shown that the nitriles used do not condense with phenol itself under the same conditions that were used for polyhydroxy phenols.

The mechanism of the Hoesch reaction has been proved.

An attempt has been made to generalize the reaction of aliphatic halides with phenols.



A convenient method for the preparation of certain phenolic acids has been found.



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